

Penile Causes of ED < Peyronie's disease & priapism

① Peyronie's disease (PD)

Def: it's a disease in which fibrotic plaque develops within the tunica albuginea of the corpus cavernosa. most common in dorsal surface. it may be calcified [that mean mature plaque].

NB Peyronie's disease = penile fibromatosis of T. Albuginea.
penile fibrosis = penile fibrosis of corporeal erectile tissue.

Etiology: (theories)

- ▶ **Congenital:** Peyronie's disease sometimes associated with other congenital anomalies [ear cartilage → Tympanosclerosis]
- ▶ **Traumatic:** Repeated minor trauma [excessive, hard intercourse] or due to using VCD = vacuum constriction device
- ▶ **Neoplastic:** PD associated with carcinoid syndrome in which there's high serotonin level that initiate fibrous tissue formation
- ▶ **Infective**
- ▶ **Miscellaneous:** Aging, Atherosclerosis, DM, B blockers.

Pathology:

① the affected area (plaque)

- ① has 2 stages early inflammatory stage then late fibrotic stage
- ② Repeated minor trauma → microvascular damage of T. albuginea layers → small haematoma → inflammatory reaction → perivascular infiltrate (Lymphocytes, Plasma cells) which may:
 - resolve completely within 6 months

OR • Turned to Fibroblast → associated with Collagen deposition → Fibrous plaque → Calcification

- ③ it affect penile curvature, physiology may induce pain due to traction or it may lead to ↓ sensation due to affection of dorsal nerves.

④ **Non affected area:** may show abnormal cavernous tissue, Abnormal collagen, ↓ elastic fibres these lead to ED due to abnormal cavernous tissue or Veno-occlusive dysfunction.

Diagnosis of PD:

History: penile pain during erection, deviation of erection, ED, penile lump.

Examination: ~~we~~ we should differentiate PD from other

Causes of deviated erection eg: hypospadias

epispadias, Congenital penile curvature,

pt with urethral instrumentation, endoscopy.

other causes of penile mass: eg: organized haematoma
syphilitic gumma, Neoplasm.

Investigations: ICI + Rigiscan :-

Rigiscan to examine erection

ICI to examine degree of deviation.

► Colour doppler sonography :

► Neurological examination to examine dorsal nerve affection.

Treatment of PD:

Non Surgical Treatment :-

► If the disease less than 18 months

► if there's no ED

► if there's minimal deviation.

Oral: [1] Tamoxifen: 20 mg/twice daily/ 3 months

inhibition of inflammatory, fibrotic response

[2] Colchicine: inhibition of Collagen Formation

[3] Vit E.

intralesional:

[1] Ca^{+} blockers: verapamil \rightarrow \downarrow Collagen secretion
alter fibroblast metabolism \rightarrow \downarrow Curvature, \downarrow plaque size

[2] Collagenase: inhibit fibrous tissue formation

[3] CST: Not successful.

physical Rx:

[1] Radiation: ↓ pain rather than correction of curvature.
- Not used in young → may lead to fibrosis
- better combined with vit E.

[2] Laser: used to destroy the plaque at the time of surgical therapy.

[3] U/S: Not effective.

Surgical Treatment of PD

disease more than 18 months, + severe deviation + ED

① Rx of the curvature:

The aim is to shorten the non affected side to equal the affected side.

② techniques: ① Nesbit's technique:

excision an ellipse of Tunica albuginea in the opposite side + suturing
advantages: the scar of ellipse add more strength with the sutures give
better long term.

② Multiple parallel plication (MPP) technique:

Multiple parallel plication sutures with no excision on the opposite side

Advantages: No excision so less Traumatic complications.

② Rx of the plaque:

▷ Removal of the plaque + grafting the defect.

▷ CO₂ laser is used for surgical removal

▷ this operation ~~Portner~~ may followed by ED due to

- damage of cavernous tissue underlying the plaque.

- inelasticity of the graft.

- pathological changes of non affected Tunica albuginea.

③ Rx of ED:

▷ insertion of penile prosthesis to correct ED
it shows very good results.

② Priapism

Def: Sustained penile erection that may not be related to sexual excitation for more than ⑥ hours.

NB prolonged erection: erection lasts for ④ hours.

* Both cases are emergency. to prevent irreversible damage of penile tissue.

pathology: Priapism affect only the corpora cavernosa

- ① From 6-12 hours: after 6 hours → ischemia → acidosis.
- ② after 12 hours: destruction of sinusoidal epithelium
- ③ From 24-48 hours: after 24 hours → thrombosis
- ④ after 48 hours → Complete fibrosis, necrosis.

Classification

Veno-occlusive

- ▶ more common, characterized by low flow
- ▶ ischemic: venous occlusion → ↓ venous return → ↓ flow → Ischemia → Pain

Arterial

- ▶ Less common, ↑ flow
- ▶ Non ischemic: Trauma to cavernous artery → unregulated ↑ blood flow → No ischemia, No pain.

Etiology:

① veno occlusive Causes:

① Iatrogenic:

- ▶ ICI of vaso active drugs: Most important, Most common, because they are very common in Rx of neurogenic ED
- eg: Papaverin, phentolamine, Prostaglandins
- 9.5% 4.3% 2.4%

▶ Oral drugs:

- Antidepressant: Trazodone, Fluoxetine, Lithium.
- Anti anxiety: Chlorpromazine
- Addictive drugs: Alcohol, Cocaine
- Antihypertensive: Prazosin, Hydralazine
- Androgen therapy
- Anti coagulant withdrawal → Rebound hyper coagulation (heparin)

② Non Iatrogenic :

- ~~Idiopathic~~ Idiopathic Common $\frac{1}{3} - \frac{1}{2}$ cases
- Inflammatory \rightarrow (Rare) eg prostatitis
- Traumatic : any pelvic or perineal trauma lead to \downarrow venous drainage by compression or thrombosis lead to Haematoma \rightarrow veno-occlusive priapism.
- Neoplastic : Malignant priapism.
- Neurogenic spinal cord injury, Dischermia \swarrow \uparrow neurotransmitters inhibition of sympathetic discharge for penile detumescence
- blood disorders: Common. sickle cell anaemia, in black people and (pediatric) \rightarrow recurrent attacks at night. sickling, sludging of RBCs at nocturnal erection + sleep associated hypoventilation (~~Leukemia~~).
- Leukemia; Multiple myeloma.

② Causes of Arterial priapism:

① Iatrogenic:

- after penile revascularization in which inferior epigastric anastomosed with corpora cavernosa \rightarrow unregulated Blood Flow.

- ICI if the needle injures the cavernosal artery \rightarrow \uparrow blood flow

- ② Non iatrogenic: Any pelvic trauma Cause injury to Cavernosal artery \rightarrow \uparrow Blood Flow.

Diagnosis:

	Veno-occlusive	Arterial
Incidence	more Common	Less Common
Trauma	May be present	Always present
onset	Acute	Delayed
Pain	Marked due to ischemia	Absent (No ischemia)
Penile rigidity	Marked	Less
Aspirated blood	dark red, \downarrow Poz of venous blood	Bright red
Duplex	weak arterial flow signals	obvious arterial flow signals
Cavernosography	Restricted venous Flow	No restricted venous Flow
Prognosis	Worse due to Ischemia	Better due to No ischemia

Treatment of Priapism

① Arterial priapism.

- ▶ Non surgical: Selective pudendal arteriography to diagnosis the condition then followed by embolization of abnormal arterial connections.
- ▶ Surgical: Selective cavernosal artery ligation.

② Veno-occlusive Priapism.

▶ Non surgical:

- Analgesic - after 4-6 hours if no improve we start:
 - ▶ insertion of needle in C. cavernosa take sample For ABG arterial blood gas.
 - ▶ then irrigation of 15-20 mL with saline till we obtain one of the followings:
 - Detumescence i.e. $BP < 50$
 - Aspirated blood → become Bright red
 - $PO_2 > 50$, $PCO_2 < 50$, $PH > 7.5$
 - ▶ if Failed we do ICI of: epinephrine or ephedrine or phenylephrine (Less S-E)
 - ▶ IF failed we start surgical operation.

▶ Surgical:

The aim is to shunt blood from Cavernosus Cavernosa to

- glans penis
- Cavernous spongiosum
- Saphenous vein.

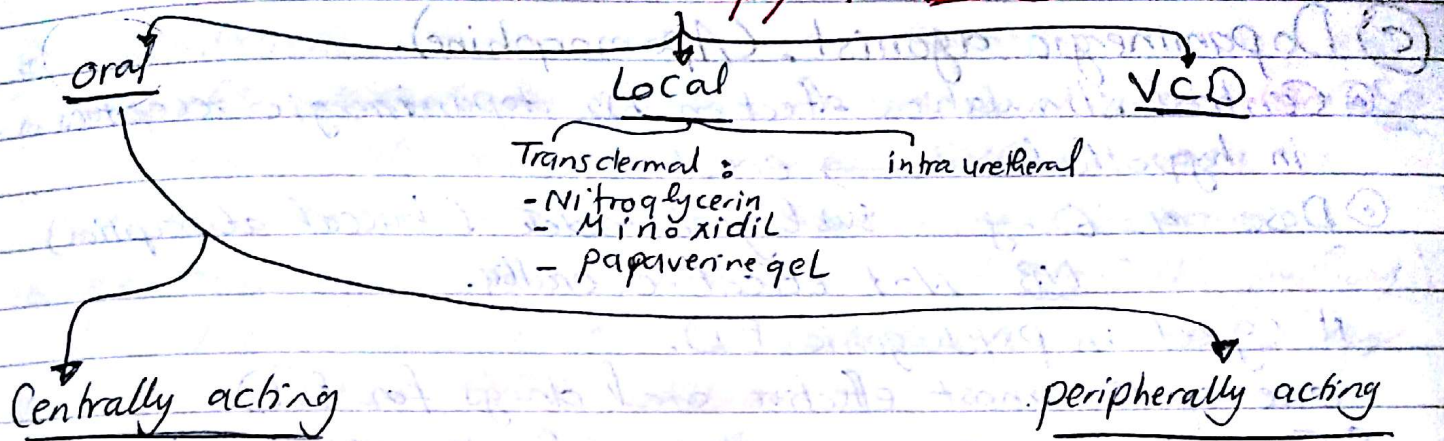
we do:

Cavernoso glans shunt

Cavernoso spongiosum shunt

Cavernoso saphenous shunt.

Non invasive therapy of ED



- ① Adrenergic blockers <
 - ② Serotonin ~~blockers~~ agonist
 - ③ Dopamin receptor ~~blockers~~ agonist.
 - ① Selective PDE inhibition
 - ② Non selective PDE
 - ③ Nitric oxide.
- ## ① Oral therapy of ED
- ### [I] Centrally acting drugs.

① Adrenergic receptor blockers:

- ▶ Yohimbine: indol alkaloid have 2 blocking effect
 - Central α -adrenergic blocking effect \rightarrow Facilitate erection
 - peripheral α -adrenergic blocking effect \rightarrow relaxation of vascular smooth muscle, corporeal smooth muscles \rightarrow Erection.

- Dose 5-10 mg / 3 times daily. good in Psychogenic ED

- S.E: Headach, insomnia, tremors, palpitation, \uparrow BP

▶ Phentolamine: (Vasomax).

- α -adrenergic blocking agent used in ICI: route in combination with other drugs.

- Have central α adrenergic blocking action, Central Anxiolytic action.

- Dose: oral 20mg-60mg

- S-E: mild: orthostatic hypotension, tachycardia, nasal stuffiness, gastric troubles it's dose related S-E

② Serotonergic Agonist (Trazodone):

- ① it has central serotonin agonist action, peripheral α -adrenergic blocking action

② Dose: 100-200 mg/day.

③ S-E: Sedation (sever), orthostatic hypotension, Prolonged erection.

① Dopaminergic agonist: (Apomorphine).

② Central stimulation effect on D₂ dopaminergic receptors in hypothalamus → erection.

③ Dose 4-6 mg sublingual tablet (buccal absorption)
NB Not effective orally.

it's good in psychogenic ED.

one of the most effective oral drugs for ED.

S-E yawning, nausea, vomiting if taken as injection.

[2] Peripherally acting drugs.

① Selective phosphodiesterase inhibitors: (Sildenafil) citrate

② Phosphodiesterase enzyme has 6 isotypes. the most important one is isotope type ⑤ which is responsible for \downarrow cGMP → \uparrow intracellular Ca^{2+} → Contraction of Corpus Cavernosa.

③ Sildenafil citrate is a selective PDE inhibitor type ⑤ so it protect cGMP → \uparrow cGMP → \downarrow intracellular Ca^{2+} by promoting Ca^{2+} to bind to Ca^{2+} binding proteins → Relaxation of C. cavernosa smooth muscle → Erection.

④ Dose: 50 - 200 mg the usual dose is 50 mg taken (0.5 - 4 hours) before coitus.

⑤ Therapeutic effects:

- ▶ it is enhancer agent rather than erection inducer
- ▶ better if taken on empty stomach.
- ▶ it's good in Psychogenic ED, less effective in organic ED

⑥ Side effects:

Headache, Facial Flushing, indigestion, Myalgia, visual disturbance, these S.E are due to presence of PDE₅ in other body tissues.

⑥ Drug interaction:

▷ Sildenafil depends on cytochrome P450 in its metabolism. So it interacts with any drugs that inhibit CYP450 as:
Ketoconazole - Erythromycin - itraconazole, Cimetidine.

▷ the action of Sildenafil depends on NO/cGMP pathway. So it's contraindicated in patients on Nitrates - 100 -

⑦ Non selective PDE inhibitors:

pentoxifylline: (Trental).

main use: ischemia

it improves ED when taken 400mg / 3 times/day / 12 weeks.

⑧ Nitric oxide Donors: (Endothelium derived Relaxing Factor)

① L-arginine (amino acid) is the precursor of NO.

② NO is synthesized from L-arginine under the effect of NO synthase in the vascular endothelium. This process depends on the presence of high P_{O_2} 100 mg/Hg. So it's occurred in Normally Flaccid penis in which ↑ Arterial blood.

Venous Blood has P_{O_2} 25 mg/Hg so it's not synthesized.

③ Mechanism of action: by

production cGMP → ↓ intracellular Ca^{2+} → Relaxation of smooth muscle → erection.

② Local therapy of ED

A) Transdermal therapy:

① Nitroglycerin: it leads to release of NO → ↑ cGMP → ↓ Ca^{2+} → Relaxation of smooth muscle → erection.

Dose: ointment 2% Before coitus it gives better response in pt with spinal cord injury.

it improves the erection but not to achieve Rigid erection due to weak absorption through thick Tunica albuginea.

Some doctors try to overcome this problem by performing a window of 1 cm² in Buck's Fascia and T. albuginea and grafting it by ~~the~~ deep dorsal vein then applying nitroglycerin oint over this graft.

Side effects of Nitroglycerin:

① headache, hypotension in both partners due to transvaginal absorption. this problem can be solved by using condom or applying the oint. in perineal area.

② Minoxidil:

main use: hypertension and androgenetic alopecia
mechanism of action: vasodilator drugs acts on opening potassium (K^+) channels \rightarrow prevent Ca^{2+} entry
 \rightarrow Relaxation of smooth muscle \rightarrow Erection.

Dose: apply 1 mL of 2% minoxidil solution on glans
it has better effect than Nitroglycerin.

③ Papaverine Gel: 15-20% gel improve erection in men with spinal cord injury.

④ Transurethral therapy: intraurethral therapy:

due to the weak absorption of local treatment due to thick Tunica albuginea there is a very good route of absorption via the distal urethral mucosa into corpus spongiosum then to the corpora cavernosa. this is known as:

Medicated Urethral System For Erection (MUSE)

it consists of an applicator with small tube 3 cm and 3 mm in diameter. the tip of this tube contain a small semisolid pellet contains 500 μ g of prostaglandin E_1 that delivered to distal urethra \rightarrow C-spongiosum \rightarrow C-cavernosa

① another form: PGE₂ cream formed by:

PGE₂ suppositories (20-40 mg) + 10 mL of 2% lidocaine gel + 40 mL surgical lubricant. is applied into urethra.

this way result in partial or full erection in 70% of pt.
Side effect of this way: Postural Hypotension.

② intra urethral drug combinations: PGE₁ + α adrenergic blockers but \uparrow hypotension S.E. MUSE is highly cost.

③ Vacuum Constriction device (VCD)

indication: Organic ED.

principles: Composed of 3 elements:

1- Vacuum chamber: or cylinder of different sizes according to penile size.

2- Negative pressure pump: it's connected to the cylinder around penis to create a negative pressure leading to rushing of blood to fill the penis → erection.

3- Tension rubber band: moved along the cylinder and put on the base of the penis to entrap the blood and keep erection. after intercourse it is removed.

NB this band should not be around the penis for more than 30 minutes to prevent vascular injury or Ischemia.

NB VCD should not be repeated with less than 1 hour interval.

Complications:

▷ Pain

▷ Ecchymosis

▷ Pulling the scrotum if the cylinder is larger than penile size

▷ Inhibition of ejaculation by the tension rubber band.

▷ Ischemia, vascular injury due to ignorance of removal of the tension rubber band for more than 30 minutes.

(1) Intra cavernous therapy ICI (2)

Injection of some vasoactive drugs into Corpora Cavernosa for both diagnostic and therapeutic indications.

⊙ Indications

[1] Diagnostic:

- ▶ Screening test: for differentiation between organic ED and psychogenic ED
- ▶ For test the erectile response of ICI in Neurogenic ED
- ▶ ~~th~~ testing the Corporo-venous ED.
- ▶ Diagnosis of penile deviation (Peyronie's disease).
- ▶ Combined with other tests of ED:-
 - it's the 1st step in vascular investigation before Duplex uls, Radioisotopes penography, arteriography, Cavernosometry, Cavernosography).

[2] Therapeutic: ICI is nearly effective for all types of ED.

- ▶ temporary therapeutic in psychogenic ED.
- ▶ Treatment of organic ED as in program of pre-coital self injection.
- ▶ it can be added that PGs that have an effect to prevent platelet aggregation and prevent collagen formation this lead to ↓ Fibrosis

⊙ Contra-indications:

Sever psychiatric pt
Sever systemic disease
Sever Blood disease (~~st~~ sickle cell anaemia, leukaemia)
Sever Peyronie's disease
Sever Corporo venous in competence.

Drugs:

[1] Papaverine

the 1st drug of choice used in ICI. acts as Ca^{+} channel inhibitor and acts as PDE inhibitor

⑥ Dose: 60-120 gm. ~~used as~~ single drug or combined

[2] phentolamine Mesylate

⑥ Competitive α -adrenergic Antagonist.

NB adrenergic neurotransmitters (~~nor~~adrenaline) results in activation of sympathetic lumbar center \rightarrow contraction of cavernous tissue \rightarrow penile detumescence

⑥ it's used as a combined therapy not single drug.

Cause it's acting as tumescence rather than rigid erection

⑥ Dose: 0.5 - 1 mg

[3] Prostaglandin E_1 [prostin VR] [Caverject]

(home use)

⑥ The only drug FDA approved for ICI

⑥ $PGE_1 \rightarrow$ vasodilatation $\rightarrow \uparrow$ adenylyl cyclase $\rightarrow \uparrow$ cAMP \rightarrow Erection. dose: 10-20 μ g

⑥ $PGE_1 \rightarrow$ prevent platelet aggregation + prevent Collagen Formation $\rightarrow \downarrow$ fibrosis.

⑥ Low systemic side effect cause it is locally metabolized

⑥ Local side effect \rightarrow Priapism, Pain R/ procaine 20mg acetate

[4] Combination therapy

Bimix: PGE_1 + phentolamine

Trimix: PGE_1 + phentolamine + Papaverine

S-E: prolonged erection that may need intervention.

Quadmix: PGE_1 + phentolamine + papaverine + Atropine \rightarrow

\uparrow Release of NO \rightarrow erection.

S-E: severe Cardiac Collapse.

side effects of ICI:

[1] Local:

- ▷ Prolonged erection (Priapism) (acute complication).
Emergency complication. It can be reduced by adding PGE₁ (1%) compared with papaverine (10%) and papaverine + phentolamine 7%.
- it can be prevented by decreasing the dose.
- ▷ Pain: is common with PGE₁ can be treated by adding procaine 20mg.
- ▷ Fibrosis: very common with papaverine. Can be reduced by adding PGE₁.
- ▷ Faulty injection: injury of urethra or sinusoidal wall that may lead to haematoma and fibrosis.

[2] Systemic: due to systemic absorption.

- ▷ Hypotension: more common with papaverine
- ▷ Hepatic toxicity: " " " "

[3] Psychological:

- o Fear of needle and injection
- o Anxiety about side effects.
- o Lack of spontaneous intercourse
- o Lack of partner satisfaction.

Surgical Treatment of ED

surgical operations:

- (1) penile revascularization in R of arteriogenic ED
- (2) penile Venoligation in R of corporovenogenic ED
- (3) penile shunt in R of priapism
- (4) penile corrective operation in Peyronie's disease in pt with severe deviation.
- (5) penile prosthesis

penile prosthesis (implant)

indications:

- ① Any patient with ED and/or deviation that prevent intercourse
- ② Failure or unacceptance of Non invasive therapies eg oral or ICI or VCD
- ③ The following organic ED conditions:
 - ▷ DM
 - ▷ Renal Failure
 - ▷ Neurogenic ED
 - ▷ Vasculogenic ED
 - ▷ Post priapism ED
 - ▷ Peyronie's with ED
- ④ patient with Psychogenic ED after failure of prolonged sex therapy and failure of non invasive therapy.

Types of penile prosthesis:

- ① Semirigid (Malleable) prosthesis: ^{double rod device. Formed of outer Silicon cylinder, inner stainless steel wire}
have 2 characters. ① rigid enough for coitus

- ② malleable enough for concealment during daily activity.
- ▷ advantages: - Low price, Low incidence of mechanical complication.
- easy surgical placement; good for Peyronie's pt.
- ▷ Disadvantages: less concealment than inflatable prosthesis
- more liability to Erosion in Neurologically pt.


② Mechanical prosthesis:

it's one type Dura II Formed of articulating segments of polyethylene and stainless steel cable passes through the center of these segments. advantages: better concealment compared with malleable prosthesis (due to preservation of it's shape in straight position during coitus and it's downward direction during daytime)

Disadvantages: mechanical damage

[3] Inflatable prosthesis:

- ① They have the advantages of semirigid and mechanical prosthesis.
 - ① they give the penis tumescence and rigidity by their inflation before coitus and detumescence and flaccidity by their deflation after coitus.
 - ① their inflation and deflation depends on a reservoir of fluid, corporeal cylinders and a pump that transverse the fluid from reservoir to the cylinders.
 - ① they are 3 types ① one piece ① two pieces ① three pieces
 - ▷ Surgically one piece more easier for implantation than 2 pieces and 2 pieces more easier than three pieces.
 - ▷ physiologically 3 pieces more better than 2 pieces more than 1 piece because the 3 pieces give the penis more tumescence and rigidity due to higher volume of fluid transferred during inflation.
- one piece inflatable prosthesis:

- ① double rod device. each rod consist of:

 - proximal reservoir cavity from which the fluid is transferred to a central mid chamber. when erection is required by pressing the distal pump inside the glans penis lead to inflation of the device.
- ① Deflation is obtained by firm steady bending of the central part of the device for 10 sec to transfer the fluid again to the mid chamber then to proximal reservoir.

Two pieces inflatable prosthesis: Formed of 2 pieces

1st piece: Corporeal cylinder in each corpus cavernosum.

2nd piece: (Reservoir and pump) in one piece [Resipump] that is fixed in the scrotum between testicles.

Three pieces inflatable prosthesis: Formed of 3 pieces

1st piece: Corporeal cylinder in each corpus cavernosum.

2nd piece: (reservoir) placed in perivesical (retropubic) space.

3rd piece: Pump placed inside the scrotum.

advantages: the 3 pieces can increase ~~the~~ in both diameter and length.

Complications of penile prosthesis:

[1] operation Complications:

- ① Inadequate Corporal dilatation: ~~an~~ insertion of too short prosthesis lead to instability of the flaccid glans penis over the distal end of the prosthesis → pain, difficult intromission
- ① Injury to penile structures:
 - ▷ Urethra: occurs near the meatus the operation should be postponed till the healing occurs.
 - ▷ Corpora cavernosa: if using thin dilator or forcing them against fibrotic area
 - ▷ Corpus spongiosum: ^{lead to} ischemic necrosis to the glans or penis if blood supply is damaged either during operation or due to tight dressing of the penis.
- ① Injury to prosthesis: by the needle during suturing.

[2] Early post operative Complications:

- ① Pain due to infection or due to insertion of too long prosthesis. Normally pain is last for 2 month after operation but if it is more than 2 month (infection, too large prosthesis).
- ① Prosthesis infection: G +ve (staph epidermidis, staph aureus) G -ve (E. coli) and anaerobic organism. CIP: Pain for more than 2 month, purulent discharge, erosion to the prosthesis.
- ① Prosthesis erosion: is more common in pt with reduced penile sensation, urethral strictures, after radiotherapy or steroid therapy. also common in semi rigid prosthesis especially if the prosthesis is too long or it's infected.

[3] Late post operative Complications:

- ① Satisfaction of Partners: may be incomplete. so reassurance should be done before surgery: ⓧ ED can be treated by oral, ICI, VCD
- ⓧ the penis will not be long as natural ⓧ prosthesis may break or infected
- ⓧ it take 1 year to achieve orgasm.
- ① Survival of prosthesis: in inflatable prosthesis last for long time not like mechanical which can be changed every 5 years.
- ① Silicone induced problems: Autoimmune diseases related to silicone.